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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/056,343	04/07/1998	UFFE LOEVBORG	3556.224-US	5207

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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1652	21

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/056,343	LOEVBORG, UFFE	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-53, 56-62, 65 and 66* is/are rejected.

7)☒ Claim(s) *54,55,63 and 64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission, Amendment C, Paper No.17 filed on November 1, 2001, has been entered. Claims 40-47 were cancelled and claims 48-66 and the Abstract submitted with Paper No. 17 were entered. Applicant's Terminal Disclaimer, Paper No. 18 filed November 1, 2001, is effective and has been entered, overcoming the obviousness-type double patenting of record stated in Paper No. 15, mailed May 1, 2001. The new claims 48, 58 and 59 present no issue of indefinite description and avoid the rejection under the second paragraph of 35 U.S.C. §112 stated in Paper No. 15, mailed May 1, 2001.

Claim Rejections - 35 USC §§102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. §102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. §122(b). Therefore, this application is examined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-50, 56-59, 65 and 66 are rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Ladner et al., U.S. 5,223,409, made of record herewith.

The claims require no particular amino acid sequence for a reference protein, do not require that a particular epitope region be altered in any reference protein, and require no particular amino acid sequence modification to reduce allergenicity. Available as prior art in view of the March 2, 1990, priority date for their disclosure in section "V.R.", column 102, line 43, through column 103, line 30, Ladner et al. set forth a recombinant method for modification of the amino acid sequence of a polypeptide, such as the medicinally active enzyme streptokinase, that is "antigenic to an undesirable extent" in order to produce a variant polypeptide with reduced allergenicity. Ladner et al. disclose a first step of preparing DNA segments encoding several "Initial Potential Binding Domains" [IPBDs] that are consecutive peptide regions of a polypeptide that is undesirably antigenic, wherein the DNA segment is comprised within a conveying DNA sequence, an expression vector, termed a "Genetic Package" [GP], permitting a host cell maintaining a GP to display each IPBD peptide on the surface of an expressed carrier molecule, a coat protein of a bacteriophage. While Ladner et al. do not use the term "epitope", the artisan reading their disclosure would recognize that the "antigenic determinants" which Ladner et al. discuss, i.e., the native IPBDs that bind most effectively in their method to a detecting antibody surface, are epitopes.

Ladner et al. disclose a second step of variegating the amino acid sequences of each of the several IPBD peptides by altering DNA segments encoding each within conveying DNA

sequences that form another set of GPs permitting the surface display of the variegated "Potential Binding Domains" [PBDs] by the host cell on an expressed carrier molecules. Ladner et al. disclose a third step of contacting both the several native IPBDs and their corresponding, variegated, PBDs with a surface covered with antibodies, preferably monoclonal antibodies, raised in a person to the polypeptide that is undesirably antigenic. Ladner et al. disclose a fourth step of measuring the binding affinity of each of the carrier molecule-displayed IPBDs, and the binding affinities of their corresponding variegated PBDs, to determine which peptide sequences of the variegated PBDs bind with reduced affinity to the antibody-covered surface and a further step of selecting those peptide sequences that bind with reduced affinity as replacements for the corresponding peptide region of the undesirably antigenic polypeptide. Ladner et al. then disclose the preparation of a DNA encoding the modified polypeptide, expressing it in a host cell to produce a modified, composite, polypeptide having reduced immunogenicity by comparison with the native undesirably immunogenic polypeptide, and capable of evoking a lower immunogenic response in an animal than the native undesirably antigenic polypeptide, and then testing it to ensure that it maintains its desired activity despite the amino acid sequence modification that incorporates a variegated peptide region replacing a native peptide region to produce a lower immunogenic response in an animal.

Ladner et al. anticipate the methods of claims 48-50, 56-59, 65 and 66 because they disclose the preparation of a DNA molecule encoding a variant of a reference protein having a known amino acid sequence, streptokinase, which is a medicinal enzyme, wherein the variant is expressly designed to evoke a lower immunogenic response in an animal, because they mutate a DNA sequence in order to design the variant and the mutation is incorporated in the synthesis of a DNA molecule, because they inherently map epitopes of the immunogenic reference protein and prepare a host cell to express the variant lacking an

epitope of the reference protein and because they recover the variant after inducing its expression by the variant. It is not considered necessary for Ladner et al. have to set forth the amino acid sequence of streptokinase, to have set forth the specific antibodies used to identify its antigenic determinants, epitopes, or to have set forth the nucleic acid sequence encoding a redesigned streptokinase with an altered amino acid sequence that evokes a reduced immunogenic response in an animal. This is because the streptokinase amino acid sequence was known in the art when Ladner et al. filed the priority application in March, 1990, and because further disclosures of Ladner et al. are more explicitly devoted to redesign and synthesis of DNA sequences encoding variants of other polypeptides. In the alternative, Ladner et al. are considered to have rendered methods of claims 48-50, 56-59, 65 and 66 obvious to one of ordinary skill in the art at the time the invention was made because they teach each step needed to practice a method set forth in the claims, order the steps in a process that will provide results the claims describe, teach a medicinal polypeptide known to evoke an immunogenic response in animals that would be more efficacious were its immunogenicity lowered, thus providing motivation to do so, and also disclose many examples of practicing each step of the method taught in section "V.R." elsewhere in the patent, with other polypeptides and their encoding DNAs, thus providing a reasonable expectation of success in practicing their methods to an artisan at that time.

Claim Rejections - 35 USC §103

Claims 51-53 and 60-62 are rejected under 35 U.S.C. §103(a) as obvious over Ladner et al., U.S. 5,223,409, as applied to claims 48-50, 56-59, 65 and 66 above, in view of either Zacharaiae et al., 1981, Allergy, Vol. 36, pages 513-516, or Arlian et al., 1990, International Archives of Allergy and Applied Immunology, Vol. 91, pages 278-284, both of record.

The claims require no particular amino acid sequence for a reference protein, do not require that a particular epitope region be altered in any reference protein, and require no particular amino acid sequence modification to reduce allergenicity. Disclosures of Ladner et al., discussed above, are taken as before. Zacharaiae et al. teach that industrial exposure

to the detergent enzymes Alcalase® and Esperase®, which are microbial subtilisins, will cause IgE antibody-mediated sensitization in persons, resulting in chronic, symptoms of respiratory irritation, coughing, shortness of breath, and chest tightening. Arlian et al. similarly teach that industrial exposure to the detergent enzymes Alcalase® and Savinase®, microbial subtilisins, will cause respiratory allergy and that both serine proteases exhibit specific, electropositive antigens that bind significant levels of human IgE antibodies as demonstrated by crossed immunoelectrophoresis. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the amino acid sequences of any of the microbial subtilisins, such as Alcalase®, Esperase®, and Savinase®, used in formulating detergent compositions for a streptokinase amino acid sequence in the method taught by Ladner et al. to identify the epitope region that provokes IgE-mediated sensitization and allergy in persons exposed to the subtilisins and to replace it with a variegated peptide region in preparing a variant capable of evoking a reduced immunogenic response. This is because the amino acid sequences of these three serine proteases were already know in the art at the time the invention was made, because a generic DNA sequence could be synthesized to encode each amino acid sequence, thus providing a basis for mutation to variegate amino acid sequences of peptide regions identified as an antigenic determinants in a method of Ladner et al., and because such an artisan at that time would have had a reasonable expectation of success in preparing a variant of any or all of these enzymes that would evoke a lowered immunogenic response in a person where suitable IgE antibodies could be isolated from exposed individuals to conduct the screening steps of Ladner et al. that identify the significant antigenic determinants and permit measuring of reduced binding to antibody to identify variegated peptides that, when replacing the antigenic determinant, or epitope, in a variant subtilisin will render the variant subtilisin capable of evoking a lowered immunogenic response in a person.

Allowable Subject Matter

Claims 54, 55, 63 and 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. While Gerber, U.S. 4,945,043, made of record herewith, discloses that an amylase - a process enzyme according to claims 54, 55, 63 and 64 - possesses epitopes, as measured by the response of one animal's immune defense system to exposure to a foreign amylase, nothing in Gerber, nor in the other prior art of record, suggests that "process" enzymes that are not "industrial" enzymes cause sensitization or allergy in those handling them to any noticeable extent. Thus the prior art provided no particular motivation for one of ordinary skill in the art, at the time the invention was made, to apply the method of Ladner et al. to a particular "process" enzyme, or class of process enzymes, to produce a variant having a lower immunogenic potential than the native enzyme.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 7:00AM-5:30PM EST on Mondays and Wednesdays, between 7:00AM-1:30PM EST on Tuesdays and Thursdays, and between 8:30AM and 5:00PM EST on Fridays. The examiner's direct FAX telephone number is 703.746.3169. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

William W. Moore
April 5, 2002

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